preventable disease, not only in sporadic cases but in outbreaks as well, challenges the public health official to overcome the barriers of indifference, ignorance and inadequate legislation. The enviable record of the United States Army, in which the incidence of typhoid fever is so low, and was so low during the World War that it is considered to be of minor importance, can be attained in civil groups, but only when there can be had the complete coöperation and earnest effort of the privately practicing physician, the public health minded laboratory worker, the sanitary engineer, and the health officer. There must be utilized, in addition to good concurrent epidemiology, health education, vaccination, modern sanitation, systematic search for and supervision over the bacillus carrier and rigid inspection and control over food establishments, particularly those serving or selling food to be eaten uncooked or without further preparation. The gap between what can be done and that which is actually accomplished in public health is wide, and we can go only as far as public opinion wants that we should go, but the goal is not unachievable.

Department of Public Health, 1095 Mission Street.

LEUKODERMA—ITS TREATMENT*

By H. C. L. LINDSAY, M. D.
Pasadena

DISCUSSION *by H. J. Templeton, M. D., Oakland; Irving R. Bancroft, M. D., Los Angeles; Harry E. Alderson, M. D., San Francisco.*

THE treatment of leukoderma or vitiligo requires not only a deposition of pigment in the areas of depigmentation, but it also requires a redistribution of pigment from hyperpigmented borders, so that the result will be an even distribution of the normal amount of cutaneous coloring. The effect of an added general coloring to a patient's skin, suffering from vitiligo, would result in a difference of color scale, as an artist would term it, with the depigmented areas a darker color, but relatively the same unless the coloring used be pitch-black. This point can be demonstrated by painting the area of a vitiligo skin with a transparent brown stain. The white areas will color brown, but the tan of the borders of lesions will be little short of black. Knowing well that the white areas are as white as they will ever be, it is possible to lessen the conspicuousness of this contrast with the surrounding skin color by bleaching the dark skin to match the white with dermatologic bleach. On the other hand, it is more difficult to tint the white areas to match the surrounding, somewhat more normal looking skin. Diluted butternut stain, such as is used for dyeing hair, is used by some patients. Others use grease paints of suitable tints, or special powders, to disguise their leukoderma.

* Read before the Dermatology and Syphilology Section of the California Medical Association at the sixtieth annual session, San Francisco, April 27-30, 1931.

INTRACTABLE NATURE OF LEUKODERMA

All methods of establishing a complete cure of leukoderma to date have been relatively unsatisfactory. Local methods are those most frequently employed to produce pigmentation in areas lacking color. Bouchi dana (psoralia corylifolia) in ointment form is that most used in India. A 10 per cent alcoholic solution of oil of bergamot, applied to depigmented areas, followed by raying of the parts by ultra-violet rays, as advocated by Berlocq, has met with favor in America. These treatments produce dilatation or congestion of the deep venous plexus of the skin which in some ways favor pigmentation.

The full effect of the action of certain rays upon cells or tissues, capable of becoming pigmented, is not perfectly understood. We know that ultra-violet rays, x-rays, radium rays, and complex sun's rays have the power of stimulating pigmentation, but this usually follows definite erythema of the parts. Light has a soothing effect on the nerves, but if the nerves of the skin be anesthetized and an exposure of it be made to ultra-violet rays, we are informed that no inflammatory reaction will take place, as might ordinarily be expected. Another point worth taking into consideration at this juncture is the chemical alteration in the tissues. This can be induced by the injection or the administration of such drugs as hematoporphyrin, sulphon methane, and acridin, which will cause the skin to burn from rays of the sun much more readily than it otherwise would; that is, these drugs induce photosensitivity. It is but reasonable to suppose that the reverse of photosensitivity can be induced by other drugs if we but knew them.

CHEMISTRY OF PIGMENT

The chemistry of pigment has been investigated by an examination of the pigment in hair, which does not apparently owe its coloring matter to any of the chemical constituents of blood. Hellmick believes, "pigment is a direct product of the epidermal cells, and is not a hematogenetic substance which has been conveyed to the epidermis by chromatophores, and that the nuclear substance is probably the mother substance of this pigment." Hooker has demonstrated the development of pigment in cells of the epidermis of frogs (ryma pipiens). The elaboration of pigment was observed in some of the epidermal cells, at first appearing as a mass of brown granules in the immediate vicinity of the nucleus. The pigment gradually spreads throughout the entire cell. After the elaboration of a considerable amount of pigment, these cells either actively or passively migrated to a position below the nonpigment-bearing cells.

It has been suggested that if the essential pathologic change lies within the restricted areas of the skin, it would be logical to endeavor to induce a change in the chemistry of the cell, possibly by proper doses of roentgen rays. There is no doubt in my mind but that a certain amount of pigment

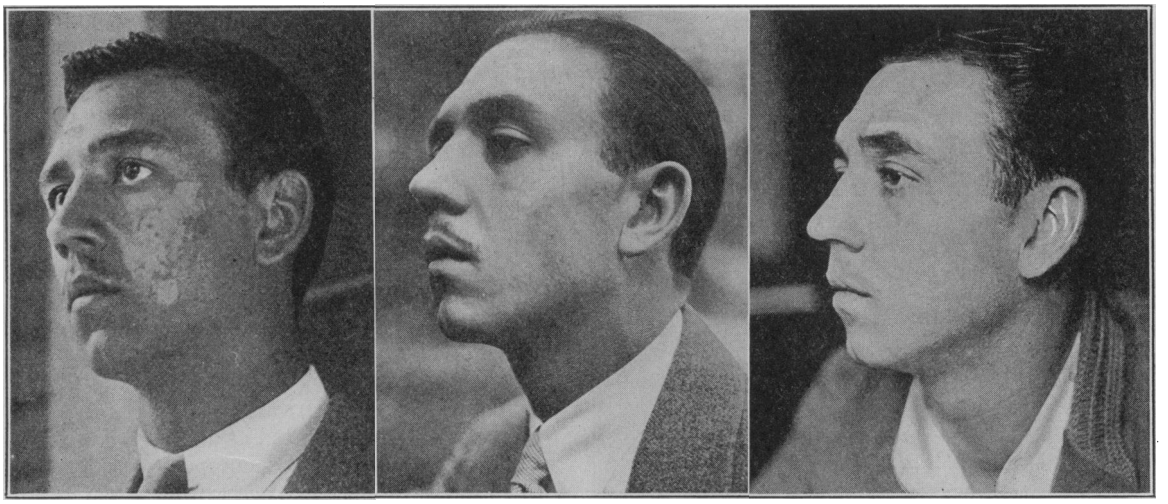

Fig. 1.—Severe recurrence of vitiligo after having been free of it for many months.

Fig. 2.—Result of three intravenous injections of 100 milligrams of gold and sodium thiosulphate, each dose.

Fig. 3.—The ultimate result of a case of vitiligo which showed recurrence and responded again to gold therapy.

is produced in the outermost layers of the skin, and that possibly these pigmentary cells have the power to migrate to lower strata; otherwise we could not expect such rapid results as can be obtained by skin bleaches, which remove the most superficial layers of the stratum corneum. Ultra-violet rays are not the only rays which stimulate active pigmentation. The skin contains a great deal of cholesterol, which is easily activated by ultra-violet rays. Cholesterol is one of the few alcohols that will easily pass through the skin, and it is found in all animal fats, in bile, in blood, brain tissue, milk, nerve fibers, the liver, kidneys, and even the suprarenal bodies. Activated cholesterol, by virtue of its power to freely pass into the skin and circulation, suggests a medium by which cells may be activated.

ACTION OF CHOLESTEROL AND OTHER CHEMICALS

Does this activated cholesterol stimulate the cells, which have the power of producing pigment, to greater activity? Will other chemicals do it?

The impression that ultra-violet rays will not cause hemolysis during life does not coincide with the findings of the following experiment. I exposed the skin of an arm to ultra-violet rays administered by the water-cooled quartz lamp and used heavy contact pressure for one hour. Immediately after the seance, the skin of the treated part showed a definite yellow color, almost a regular tan. This could hardly be expected from melanoblasts or chromatophores in such short time, and I regard it as a result of hemolysis.

If rays of light be passed through a photographic plate or negative upon sensitized photographic paper, it will be found that wherever the negative is clear of coloring matter the sensitized paper will become rapidly darkened, but wherever the negative is darkened the sensitized paper (*i. e.*, the positive, underneath) will remain practically unchanged. By watching through the negative, as it is superimposed upon the positive, in a good light for a sufficient time, the whole area will appear practically black. If at this time the sensitized paper be "fixed" by "hyposolution," the areas underneath the dark parts of the negative will still be found lighter than the other parts of the positive. It appears to me that repigmentation in leukodermic skin follows in principle many things observed in photography. The biochemistry is too complex for explanation at present, but we do know that we must have repigmentation in the areas of depigmentation with a relative lessening of pigmentation in the hyperpigmented areas; in other words, an averaging of the pigmentation. This seems to be accomplished in some instances by the injection intravenously of gold sodium thiosulphate. Both hyposulphite of soda and gold are used in photography. The former as a "fixer" and the latter as a "toner." Repetition of circumstances which favor the development of leukoderma in an individual will often result in a recurrence of the condition. Thus I have had one patient develop vitiligo three different times, as follows: Each time it occurred during the first week of the swimming season, when the full blast of the sun's rays would meet no mitigating obstruction. This patient recovered the last time by the injection of three doses of gold and sodium thiosulphate intravenously. Recurrences are to be expected, but this is not always the case. It should be admitted that some patients respond slowly to treatment and some have delayed results, that is, no apparent results visible until further treatments seem useless; as in one instance, the patient had been given up as not amenable to the gold therapy, when a surprising improvement occurred. Unfortunately this type of treatment is not always of much benefit in cases which are not attributable to photosensitivity, although it has improved a few patients whose conditions were not traceable to definite causes. It is probable that the gold would, at least, benefit those cases associated with syphilis or tuberculosis, and I have found its best results in those who had symptoms of mild hyperthyroidism.

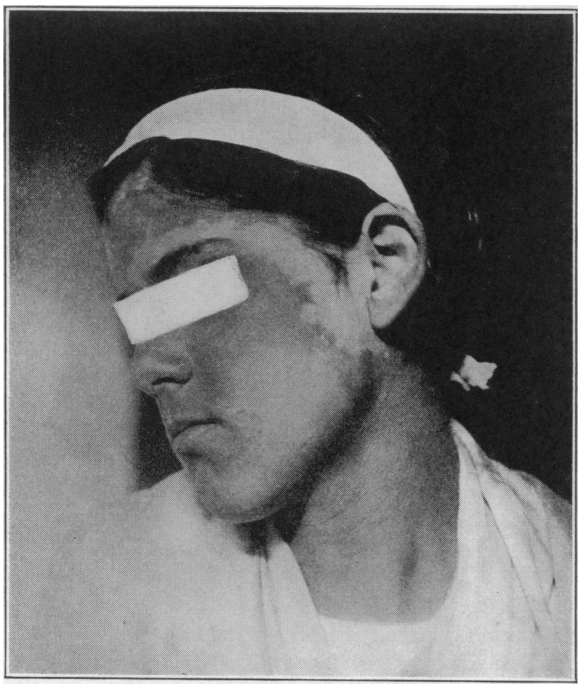

Fig. 4.—Recurrence of vitiligo in a case formerly improved by gold therapy.

DISTURBANCES OF METABOLISM

Metabolic disturbances are causative or associated with leukoderma. Among the conditions to be considered are: hyperthyroidism, Addison's disease, pregnancy, syphilis, especially syphilitic involvement of the vegetative nervous system, chronic intestinal infections, tuberculosis, and leprosy. It will give the biological chemists an immense amount of work to reconcile facts with their theories, but in all probability the cause of leukoderma will be found in disturbances which affect one or all of (*a*) some part of the nervous system, (*b*) the chemistry of the tissues in its relation to (*c*) rays of the sun or some other factor from without. Most of the diseases which are associated with leukoderma (aside from those already mentioned) are skin diseases of somewhat indeterminate origin, such as pityriasis rosea, alopecia areata, pityriasis lichenoides chronica, morphea, lichen planus (white spot disease), and psoriasis. Most of them have scales and some obscure nervous manifestations or idiosyncrasy toward rays of some sort, more especially x-rays. Thus pityriasis rosea only involves practically the covered parts of the body, and one good generalized artificial sun bath will cure many cases within a few days. On the other hand, a heavy dose of x-rays directed on the back between the shoulders will frequently clear a case of lichen planus (white spot disease). A similar dose of x-rays over the region of the parathyroids will sometimes clear a case of psoriasis for many weeks. Then, too, scaling skin diseases such as ringworm, pityriasis facialis, and pinta of fungus origin, occasionally show leukodermic areas. It is now believed that either the fungus, or a toxin from the fungus, enters the circulation and produces the so-called phytids. When examined by ultra-violet rays under a Wood's filter, these fungi are fluorescent. Tricophytids are considered, by some dermatologists, as due to allergy. Achromia parasitica is supposedly due to aspergillus. Dixon considered that pigmentation may be concerned with chemical changes in the skin which fluoresce under the same rays that cause erythema. It is a well known fact that "diabetics" sun-burn readily. Treatment of leukoderma where it complicates, or is caused by another disease, may clear up if the condition, other than the vitiligo, is treated. Thus, infections of the intestinal tract, *Entameba histolytica* and the organisms of bacillary dysentery, gas-forming organisms like *Bacillus lactis aërogenes* and *Bacillus acidi lactici,* which cause intestinal decomposition destroying catechol bases should, according to Acton, be treated by intestinal antiseptics. I am informed by Lieutenant Colonel A. W. Acton, C. I. E., I. M. S., director of the School of Tropical Medicine and Hygiene of Calcutta, that over 30 per cent of his leukoderma patients in India have some sort of defect in the gut. He has had over a thousand cases of leukoderma and believes that a great deal can be done to cure it, in that country, by the use of intestinal antiseptics. One of his favorite remedies for this purpose is liquor hydrargyri perchloridi, used internally.

SOME EAST INDIAN THERAPY

While many are not convinced that Bloch's theory of pigmentation is correct, still in India, native physicians, who follow the teachings of Ayurveda, recommend a diet free of fat, but consisting largely of chic pea. Chic pea contains a

Fig. 5.—Definite improvement in a case of recurrent vitiligo by the readministration of gold and sodium thiosulphate intravenously.

large amount of the amino acid 3-4 dioxyphenylalanin, which Bloch calls "dopa." In short, they feed their patients "dopa" while they keep the intestinal tract antiseptic as far as possible. Owing to the fact that many cases in India show evidences of hyperadrenia, as evidenced by the insulin and adrenalin tests. Acton has used adrenalin treatment in an effort to depress the adrenal glands. Sometimes he uses adrenalin empirically where no *Entameba histolytica* can be demonstrated in the bowel.

P. Bhaskara Rau, L. M. P., Medical Officer, Local Fund Hospital, Narasapatam, Vizagapatam District, India, strongly advocates the following ointment to be applied locally:

℞ Orpiment .....1 part
Psoralia corylifolia .....4 parts

Both are to be finely powdered, mixed and made into a thick paste by the addition of sufficient cow's urine. This is applied freely, and it is reported to have cured some cases in a week. The remedy is irritating, sometimes causing blisters if too vigorously used.

Many local remedies such as chrysarobin, and even calamin lotion, have been blamed for an appearance of areas of leukoderma. Poison ivy (*Rhus toxicodendron*) is an offender in this respect, but I suspect many other plants, too. Avoidance of these things by a person subject to leukoderma would seem reasonable. However, I have found that a case of leukoderma affecting the skin about the anus cleared under chrysarobin administered in ointment form for the purpose of curing an intractable pruritus, complicated or possibly caused by epidermophyton. On the other hand, I have used calamin lotion, tinted with ichthyol to disguise spots, and have never noticed any untoward results.

INTRAVENOUS TREATMENT OF VITILIGO

Intravenous injections with soluble dyes have been tried out by Japanese dermatologists or therapeutists with some success. A one per cent solution trypflavin has been most generally used in five cubic centimeter doses twice a week. The spots are then treated by exposures to ultra-violet rays. Patients thus treated have remained apparently cured for many months. I have never used methylene blue nor trypflavin, but reports of results seem encouraging. However, I have treated cases of vitiligo, diagnosed as being definitely the result of exposure to sun's rays, by intravenous injections of gold sodium thiosulphate.

It is well known that gold medications are toxic and cannot be administered without due caution. Great divergency exists in the action of gold in different individuals. A hundred doses of gold sodium thiosulphate were given one patient, without harm, in practically a hundred weeks (Bechet). Again, another case received 0.3 gram doses, for several doses, at four-day intervals, without injury. On the other hand, I have seen a violent reaction from a single hundred milligram dose. This dose is very efficacious in the therapy of conditions for which gold sodium thiosulphate is used. However, so many reactions have occurred that the Abbott Laboratories are now putting up some ampules, each containing twenty-five milligrams of gold sodium thiosulphate. These reactions to the drug are seldom serious and serve to warn us not to continue the same dose. Violent reactions can be avoided to a large extent by commencing with smaller doses and gradually increasing the same. Observation of nervous manifestations, temperature, pulse rate, intestinal symptoms, and skin changes for possible indications of intolerance should not be neglected, and in case toxic symptoms seem to be pending, the antidote sodium thiosulphate can be administered. Many thousands of doses of gold sodium thiosulphate have been given in the United States, with very few deaths reported from its use. I doubt if it be more toxic than neoarsphenamin. Personally, I have never given more than twenty doses of gold sodium thiosulphate to a single patient. Usually, I have used the hundred milligram dose after the third injection, which some physicians declare is the critical one, though I have not found it so. Post-mortem examination of a patient who had received sixteen doses of gold sodium thiosulphate, revealed no pathology in the kidney, intestine or liver; death was due to an entirely different disease from leukoderma. I had the post-mortem done on this case by an expert in this work, and a check-up of the chemical findings by two laboratories of unquestionable repute.

We must regard leukoderma as a difficult disease to handle. If we paint spots or bleach the surrounding skin, the drugs used must not be too toxic, and since the bichlorid and subchlorid of mercury are often used for this purpose, it is well to guard against dermatitis venenata (medicamentosa). Lead white washes are as a rule to be discouraged. Aside from being poisonous, they are sometimes incompatible with modern facial cosmetics and thus may stain the skin the wrong color. X-rays as demonstrated by Cleveland of Vancouver, B. C., can be used in treatment of a small area, but the safety of Berlocq's technique of correcting the malady will appeal to most of us; however, the latter method has limitations. Treated syphilis or other diseases directly or indirectly causative of vitiligo may show marked improvement in the fundamental condition before any salutary headway is detected in the vitiligo, which may remain for years.

The injection intravenously of dyes, with the object of "sensibilizing" the tissues, offers a ray of hope to the unmarried sufferers of leukoderma in the Orient, where the disease is an unsurmountable barrier to marriage. The use of gold sodium thiosulphate, carefully administered, is justifiable in the treatment of suitable cases of leukoderma. This treatment has many virtues aside from its use in lupus erythematosus, lupus vulgaris, erythema induratum, acnitis, and tuberculosis of different parts of the body. Certain gold salts have a soothing effect upon nerves and cases of photosensitivity of the skin, other than leukoderma, where pain or discomfort have been bothersome

from the sun's rays. Gold bromid is considered one of the best and most valuable of the older remedies in controlling Parkinson's disease. Other bromid salts are not so helpful. Most patients to whom I have administered gold sodium thiosulphate have improved in general health. Considering these points, I hope that more of you will try out the gold sodium thiosulphate treatment for leukoderma in those cases which you attribute the cause to photosensitivity. Reports so far by those who have used this treatment on their patients have not been encouraging as a total; no results, or incomplete cures, recurrences, and reactions have been recorded. When one considers the centuries we have had no reputable remedy for leukoderma or vitiligo, we should at least give gold sodium thiosulphate a careful trial where the severity of the condition warrants it.

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DISCUSSION

H. J. Templeton, M. D. (3115 Webster Street, Oakland).—Doctor Lindsay's usage of the terms "vitiligo" and "leukoderma" as synonymous is rather foreign to my conception. To me, the term "leukoderma" has been a general one embracing all of the depigmentations of the skin, while the term "vitiligo" has applied to a very definite clinical entity.

The symptomatic leukodermas, which arise secondarily to psoriasis, pityriasis rosea, and other scaly dermatoses, frequently disappear spontaneously. Hence it is difficult to evaluate gold therapy or any other therapy in such instances. I have seen psoriatics develop leukoderma in spite of the Vienna method of treatment, viz., ultra-violet radiation following sensitization to light induced by intravenous injections of trypaflavin.

True idiopathic vitiligo rarely responds to any form of treatment. I have treated six such cases with gold sodium thiosulphate. Although I was encouraged by the early results in one of my first patients the improvement ceased and failed to occur in the other patients. It is true that I did not give any of my patients the number of injections given by Doctor Lindsay. After having given six or eight injections in each case, I became discouraged because of the lack of improvement and discontinued the method.

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Irving R. Bancroft, M. D. (812 Detwiler Building, Los Angeles).—Doctor Lindsay suggests the possible connection between leukoderma or vitiligo and glandular dysfunction. It is well known that glandular changes are responsible for different color schemes in animals. The gonads, especially, seem to govern the brilliancy of the external covering of animals, especially birds. Thyroid hypofunction is sometimes accompanied by diffuse areas of depigmentation.

The normal balance of the vagosympathetic system is necessary for normal glandular or cellular physiology, and vitiligo, as I see it, is a semaphore which points to a natural fragility of the vagosympathetic balance. Vitiligo is frequently found in certain families and also it is found sometimes in connection with alopecia areata, exophthalmic goiter, trophic disturbances of the extremities, and in mental diseases. Vitiligo definitely resembles alopecia areata in that some cases of each disease get well with or without treatment and others do not under any known treatment.

I have found that the administration of adrenal gland substance for long periods of time is sometimes followed by recovery. Whether these patients would have recovered anyway, I do not know, but this method would seem rational because we definitely know that hypoadrenal secretion is followed by diffuse hyperpigmentation. Theoretically, the reason for this is that the normally functioning adrenal gland removes the dopa-like substance with which develops the melanin from the melanoblasts. In vitiligo we have a definite lack of melanoblasts in the affected area, and for that reason rational treatment should go back to something more basic than any local treatment. The most basic or fundamental suspect at this time is the vagosympathetic system, and it is possible that various internal remedies influence the tone of that system, but, as far as I can see, all treatment of vitiligo is a trial-and-error system of logic.

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Harry E. Alderson, M. D. (490 Post Street, San Francisco).—Pigmentary disturbances, excepting those few produced by local causes too numerous to mention, are always symptomatic. Therefore, these patients always call for very careful general medical and laboratory investigation in order to be able to treat the same on a rational basis. Occasionally I have found definite indications for organotherapy, and in such patients, after a long period of faithful medication, have seen the symptomatic vitiligo or the chloasma respond favorably. There are patients, however, in whom, in spite of most painstaking investigation, the underlying pathology cannot be found. New discoveries and developments some day, no doubt, will clarify this situation. Until then an occasional patient will have to be treated empirically.

Of local measures, of course the ultra-violet light and various irritating chemicals which ordinarily stimulate pigment production may be tried, but the results are apt to be disappointing. I have tried the combination of various photosensitizing agents with ultra-violet light in these patients, with poor success. The local use of oil of bergamot and other oils for this purpose, in my experience has been successful only occasionally.

As for the gold injections, I have not tried them, for I can see no rational basis for this form of therapy in this condition. The method is not without danger. I have given thousands of gold injections for various forms of skin tuberculosis and have seen no phenomena that suggested any influence upon the pigment-producing mechanism excepting in one patient. This was in a young man with lupus erythematosus of the face. After a series of injections his lupus erythematosus lesions improved greatly, but numerous hyperpigmented patches came on the face only. Whether or not the gold had a photosensitizing effect I do not know. We are looking for the patient's return, when we shall investigate the matter. Doctor Lindsay's discussion is very interesting, and he should be commended for presenting a question that is a source of much worry on the part of a very large number of individuals.

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Doctor Lindsay (Closing).—The rationale of treatment of vitiligo or leukoderma has been touched upon in the "Treatment of Leukoderma with Gold Sodium Thiosulphate," which appeared in the *Archives of Dermatology and Syphilology*, Vol. 20, pp. 22-26, July 1929. It must be explained that the terms "vitiligo" and "leukoderma" have been used synonymously in this article.

The definition of vitiligo is given in the fifteenth edition of the American Illustrated Medical Dictionary published by W. B. Saunders Company in 1930.

Vitiligo (vit-il-i-go), pleural Vitiligines (Latin): "A skin disease attended with the formation of smooth, light-colored patches. It occurs in youth and adult life, called also pie-bald skin and leukoderma." However, modernists have begun to consider vitiligo as an acquired condition, whereas leukoderma is regarded as "Abnormal whiteness or albinism, in patches, a congenital lack of normal pigmentation of the skin, especially that which is partial."

I believe Doctor Templeton will find that the patient who responded somewhat to gold therapy will in the long run improve, and I would like to hear from him in the future concerning the ultimate result.

The pigmentation developed in a case of lupus erythematosus which had been under treatment with gold sodium thiosulphate by Doctor Alderson I have observed in other patients, and I am of the opinion that the increase of pigment in this instance is in some way connected with the action of the drug on such a patient. It must be remembered that lupus erythematosus is a highly photosensitive disease of the skin. I also believe that certain types of vitiligo and lupus erythematosus are somewhat related.

The point which I have stressed is that vitiligo may recur after apparent cure, and in two patients whose pictures I have shown you I was able to improve them again by readministration of gold and sodium thiosulphate. A definite amelioration of the vitiligo took place within one week in one patient's appearance after a single dose of the gold. This patient had two subsequent attacks of the vitiligo spaced about a year apart, and response to the treatment of each recurrence was just as spectacular as when the gold sodium thiosulphate was used for the first time.

Investigation of the biochemical reactions of gold and sodium thiosulphate in tissue is being studied at the present time by a reputed expert in this phase of chemistry, with special reference to its action in photosensitive cases, but at the time this article is written the work is but partially finished.

THE LURE OF MEDICAL HISTORY *

ESSAYS ON THE HISTORY OF EMBRYOLOGY†

THE RISE OF EXPERIMENTAL EMBRYOLOGY

By A. W. MEYER, M. D.
Stanford University

VIII

LEEUWENHOEK

ALTHOUGH Leeuwenhoek wrote in 1682 to the Royal Society, saying "I find in the seed of man, as also of a dog, two different sorts of animalcules, answering the different sexes of male and female," it would be wrong to conclude that this statement was based on a random guess. It is true that he reiterated it and was firm in his belief in animalculism, but his espousal of the latter was based upon many observations and experiments. Leeuwenhoek had no difficulty in finding multitudes of spermatozoa in the vaginae, uteri, and the tubes of various animals at different intervals after coitus, but he failed to find anything answering to an ovum. He examined the reproductive organs of mammalian females of various species both before and after coitus, and examined and injected the uterine tubes in order to learn something about the size of their lumina. He rightly concluded that any object so large as a Graafian follicle could not possibly pass through the tubes and enter the uterus. He also stated that the so-called ova of de Graaf could not be isolated at any time in their development and declared in this connection: "I know some men will even swear that they have found the aforesaid eggs in the tuba fallopiana of beasts. But I need not believe that these round bodies they have seen in it should be drawn from the imagined egg-branch, through the long and very narrow passage of the tuba fallopiana, because some of the bodies are as large as a pea, nay as the whole egg-branch, and of a very firm and compacted substance: but the way through which they should pass is no wider than the compass of a small pin. Again if it were so as is said, these bodies would be found, not by chance, but always when searched for immediately after copulation; but that is so far from being true that it is hardly to be imagined, if we consider how little time is taken up in the copulation of several animals, as a cow, rabbit, etc. In which so short time, nevertheless, ought to be drawn down through a long and narrow passage, a great number of bodies; in some cases two or three, in others six or eight, and more, according to the number of fetuses to be produced."

Leeuwenhoek made a careful attempt to discover an ovum in the Graafian follicles and says that he even showed the "matter contained in the water bladders, which was nothing but transparent moisture mixed with some red blood globules," to a man who had been a companion of de Graaf, to demonstrate to him that the Graafian follicles were not ova as de Graaf claimed. Leeuwenhoek probably was unfortunate in opening immature follicles but he also opened some that were nearly mature, for he says that they looked red. In regard to these he says that when he examined them with a microscope he "saw they were water bladders, one redder than another, and containing some bloody matter, which consisted of glandulous parts, joined together with membranes, having many globules of blood spread among them, by which one of them was become blood red." From this it is evident that Leeuwenhoek, like many of his successors, including Haighton who also was unsuccessful in his search for ova a century later, were decidedly unlucky, for the ova of the mammals which they studied lie within the range of visibility. Since these men were used to "bend their sight," one can only surmise that they failed to recognize the mammalian ovum because it frequently is surrounded by granulosa cells when it is discharged from the ovary. The earlier investigators may also have looked for a larger body although Haighton (1797) knew the size of the blastocyst in the tube and realized that it grew larger as it descended to the uterus. Since the eggs of birds and reptiles are relatively large and also increase in size with the size of the animal, the absence, in mammals, of anything resembling them or the eggs of fish and amphibia, must have been very puzzling. Moreover, the idea that the early mammalian ovum probably was transparent was widespread and also quite generally accepted. Hence a more or less opaque body such as the ovum in the Graafian follicle of some of the domestic mammals such as the dog, for ex-

* A Twenty-five Years Ago column, made up of excerpts from the official journal of the California Medical Association of twenty-five years ago, is printed in each issue of California and Western Medicine. The column is one of the regular features of the Miscellany Department of California and Western Medicine, and its page number will be found on the front cover index.

† This is the eighth paper of a series of essays on this subject. Previous papers were printed in this journal as follows: Part I, in December California and Western Medicine, page 447; Part II, in January number, page 40; Part III, in February number, page 105; Part IV, in March number, page 176; Part V, in April number, page 241; Part VI, in May number, page 341; Part VII, in June number, page 394.